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EXAMINER
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ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/761,782	LIVSHITS ET AL.	
	Examiner	Art Unit	
	Kathleen M Kerr	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) *9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3,4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Application Status

1. In response to the previous Office action, a written restriction requirement (Paper No. 9, mailed on June 24, 2002), Applicants filed an election received on July 24, 2002 (Paper No. 10). Claims 1-9 are pending in the instant Office action.

Election

2. Applicant's election with traverse of Group I, Claims 1-8, in Paper No. 10 is acknowledged. The traversal is on the ground(s) that the Office has not supported reasons and/or offered examples supporting the conclusion that Groups I and II are related as product and process of use. This is not found persuasive because Groups I and II are, in fact, related by product and process of use since the bacterium used to make valine in Group II can also be used to recombinantly produce the mutant enzyme encoded by the DNA of Group I as previously noted. This proposed process of producing mutant enzyme is materially different from the claimed process of making valine by virtue of its method steps and its products produced. Groups I and II are classified in different class/subclasses; therefore, a search of both Groups is not co-extensive and would present a search burden on the Office to be searched together. As previously noted, the method claims of Group II would be subject to rejoinder if product (used in the methods) claims are found allowable.

The requirement is still deemed proper and is therefore made FINAL. Claims 1-9 are pending, Claim 9 is withdrawn from consideration as a non-elected invention. Claims 1-8 will be examined herein.

Priority

3. The instant application is granted the benefit of priority for the foreign application 2000101678 filed in Russia on January 26, 2000 as requested in the declaration. Receipt is acknowledged of papers submitted under 35 U.S.C. § 119(a)-(d), which papers have been placed of record in the file. Said papers are *not* in English.

Information Disclosure Statement

4. The information disclosure statements filed on April 9, 2001 (Paper No. 3) and June 4, 2001 (Paper No. 4) have been reviewed, and their references have been considered as shown by the Examiner's initials next to each citation on the attached copies. The information disclosure statement filed on October 31, 2001 (Paper No. 8) citing other pending patents by Applicants is also noted.

Drawings

5. The drawings filed on July 3, 2001 (Paper No. 6) have been approved by the Draftsmen and are, therefore, entered as formal drawings acceptable for publication upon the identification of allowable subject matter.

Compliance with the Sequence Rules

6. By virtue of the sequence listing filed on August 1, 2001 (Paper No. 5) in computer readable form and paper copy, the instant application fully complies with the sequence rules. However, there are inconsistencies noted below in Objections to the Specification that may require amendment to the sequence listing.

Objections to the Specification

7. In the specification, the Abstract is objected to for being in an improper format. The Abstract must contain complete sentences. Also, the Abstract is objected to for not completely describing the disclosed subject matter (see M.P.E.P. § 608.01(b)). It is noted that in many databases and in foreign countries, the Abstract is crucial in defining the disclosed subject matter, thus, its completeness is essential. The Examiner suggests the inclusion of a reference to mutants of *E. coli* acetohydroxy acid synthase isozyme III (AHAS III).

8. The specification is objected to for the following typographical errors. In the Abstract on page 37, line 4, "actohydroxy" is misspelled; the proper spelling is ---acetohydroxy--- as found throughout the specification. Also, in the Abstract on page 37, line 4, "isozime" is misspelled; the proper spelling is ---isozyme--- as found throughout the specification.

9. The specification is objected to for confusing descriptions of disclosed sequences, SEQ ID NOs: 5-9. On page 21, SEQ ID NOs: 5 and 6 are described as being in Figure 1. However, the sequences in Figure 1 are not identified by SEQ ID NO since they are not subject to the sequence rules. Moreover, SEQ ID NOs: 5 and 6, as found in the sequence listing, are not the unlabeled sequences in Figure 1. Also, SEQ ID NOs: 5 and 6, as described in the sequence listing, are not accurately described elsewhere in the specification; all sequences listed in the sequence listing must be described in the specification to clarify their inclusion in the sequence listing. Applicants are required (1) to correct the reference to Figure 1 and (2a) to describe SEQ ID NOs: 5 and 6 in the specification to clarify their inclusion in the sequence listing OR (2b) remove SEQ ID NOs: 5 and 6 from the sequence listing.

Also on page 21, SEQ ID NOs: 7 and 8 are referred to as in Figure 2 while the drawings specifically note SEQ ID NOs: 5 and 6. The drawings appear to have a typographical error since the sequences depicted in the figure are listed in the sequence listing under SEQ ID NOs: 7 and 8. Thus, the Examiner suggests amending the drawing (Figure 2) to delete reference to "SEQ ID NO:5" and "SEQ ID NO:6" and substitute with identification of ---SEQ ID NO: 7--- and ---SEQ ID NO:8--- (see M.P.E.P. § 608.02(p) for amendments to the drawings).

10. The specification is objected to for having inconsistent and unclear data. On page 22, the Asn29Tyr mutant is described as *ilvH3* and the Asn29Lys mutant is described as *ilvH4*. However, on page 24, the reverse is described with Asn29Lys being called *ilvH3* and Asn29Tyr being called *ilvH4*. The identification of the mutants must be clarified.

Claim Objections

11. Claims 1, 3, and 4 are objected to for the following typographical errors:

a) In Claims 1, 3, and 4, the word "actohydroxy" is misspelled; the proper spelling is ---acetohydroxy--- as found throughout the specification.

b) In Claim 3, "Escherichia coli" should be italicized as found in Claim 1 for consistency in the claims.

c) In Claim 3, lines 2-3, "free from a inhibition" is improper English and should read ---free from inhibition---.

Appropriate correction is required.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 1-2 and 4-8 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The exact nature (sequence) of the claimed DNA is unclear by virtue of the confusing language in Claim 1, line 1, of "a small subunit of acetohydroxy acid synthase isozyme III originating from *Escherichia coli*" which is defining the sequence that is mutated to meet the claim limitations. This clarity issue relating to sequence and positions numbers is mute in Claim 3 due to the entire lack of reference to structure.

The specification discloses only a single member (SEQ ID NO:2) of the genus of small acetohydroxy acid synthase (AHAS) isozyme III subunits native to *E. coli* and the DNA encoding said small subunit (SEQ ID NO:1). However, the article "a" in the phrase "a small subunit" indicates that a group of these subunits are known (the article "the" would indicate a single one known as described in the specification). The phrase "originating from *Escherichia coli*" is also unclear if it limits the DNA to a naturally-occurring sequence or if the sequence can be mutated after having been obtained from *E. coli*. Thus, the nature of the sequence to be mutated is unclear as to its metes and bounds.

In addition to the lack of clarity of the unmutated sequence, the scope of mutations allowed is also unclear. In Claim 1 (line 3), the limitation of "**a** mutation" (emphasis added) indicates that a single mutation (or mutation pair) is encompassed, but the specification notes that additional "substitution, deletion, insertion, addition, or inversion" are also included in the

scope of the claim (see page 9). It is unclear, for example in Claim 1, if the claimed DNA is limited to encoding SEQ ID NO:2 with a mutation at Ser17 or Ser17/Gly14 *only* or if other mutations of SEQ ID NO:2 are also encompassed. Also, the limitation of "corresponding to", while implying a relation to SEQ ID NO:2, does not have clear wording.

The instant claims will be herein given their broadest reasonable interpretation for prosecution purposes. Claim 1 is broadly limited to *any* DNA encoding a small subunit of AHAS III (as defined by the activity of the small and large subunits together and not a sequence) wherein positions 17 or 17/14 (corresponding to SEQ ID NO:2) are not Ser or Ser/Gly, respectively. Claim 4 is limited to *any* DNA encoding a large and small subunit of AHAS III (as defined by their activity together and not a sequence) wherein positions 17/14 or 29/14 or 91-163/14 (corresponding to SEQ ID NO:2) are not Ser/Gly or Asn/Gly, or varied/Gly, respectively. In both Claims 1 and 4, the sequence is limited to having "originated from" a sequence encoding SEQ ID NO:2 (the *E. coli* sequence disclosed); however, one or more additional mutations (substitutions, insertions, etc.) in the sequence also meet the claim limitations, as prescribed on page 9 of the instant specification. Thus, no art-limiting definition of structure is found in the instant claims.

The Examiner suggests the following claim language for Claim 1:

---1. An isolated DNA molecule encoding a mutated small subunit of acetohydroxy acid synthase isozyme (AHAS) III originating from *Escherichia coli*, which mutation is selected from the group consisting of:

a) a mutation that replaces the serine residue at amino acid number 17 in SEQ ID NO:2 with an amino acid other than serine and

b) a mutation that replaces both (i) the serine residue at amino acid number 17 in SEQ ID NO:2 with an amino acid other than serine and (ii) the glycine residue at amino acid number 14 in SEQ ID NO:2 with an amino acid other than glycine,

wherein the unmutated sequence of AHAS III is SEQ ID NO:2.---

Similar language would also be effective in clarifying Claim 4.

13. Claims 4-5 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "delete a C-terminal region from the amino acid number 91 **downwards**" (emphasis added) is unclear. Is the entire C-terminal region from residue 91 to the C-terminal end deleted? Or can any of residues corresponding to any one of 91-163 be mutated to a stop codon to delete any portion of this C-terminal region? If the first interpretation is appropriate, the claim language should limit to mutating residue 91 to be encoded as a stop codon. If the second interpretation is appropriate, the claim language should limit to mutating any of the C-terminal residues from residue 91 to the C-terminal end of the protein to be encoded as a stop codon. Appropriate clarification is required.

Also, the Examiner notes that on page 3 of the specification, a mutation of Gln92 (not 91) to a stop codon is described. This is together with a discussion of Asn29Lys, also in Claim 4. Applicants should consider whether residue 91 or 92 is the intended truncation position.

14. Claim 5 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 5 is confusing for its description of residue 29 as originally an aspartic acid

(Asp) while in Claim 4, in SEQ ID NO:2, and in the specification, residue 29 is an asparagine (Asn). Appropriate clarification is required.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 1-2 and 6-8 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claims are drawn to DNA or host bacterium wherein the DNA is claimed (a) without any *clear* structural limitations and (b) without any functional limitations. The vague structure is noted above in the rejection of Claims 1-2 and 4-8 under 35 U.S.C. § 112, second paragraph. The function of the unmutated small subunit is to act as a regulatory protein (an activator) on the catalytic activity of its enzyme partner (the large subunit); the function of the mutated small subunit is not described as a claim limitation.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed.

Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

In the instant specification, the gene encoding the small subunit of acetohydroxy acid synthase (AHAS) isozyme III native to *E. coli* is structurally and functionally described as SEQ ID NO:1 (encoded protein is SEQ ID NO:2), a regulatory subunit subject to feedback inhibition by valine. The instant claims are drawn to a genus of DNA encoding **any** small subunit having any function, without any particular structural limitations except for point mutations relative to SEQ ID NOs:1/2 as interpreted above. The limited examples of particular mutations in SEQ ID NO:1 do not adequately describe the entire genus because the structure of other members of the genus cannot be predicted based on the disclosure since common characteristics among members of the genus have not been described.

16. Claims 3-8 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 3 is drawn to DNA claimed solely by the function of the encoded proteins, both small and large subunits as defined on page 7 of the specification, without any clear structural limitations whatsoever. Claims 4-5

add unclear structural limitations as noted above in the rejection of Claims 1-2 and 4-8 under 35 U.S.C. § 112, second paragraph.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

In the instant specification, the gene encoding the small subunit of acetohydroxy acid synthase (AHAS) isozyme III native to *E. coli* is structurally and functionally described as SEQ ID NO:1 (encoded protein is SEQ ID NO:2), a regulatory subunit subject to feedback inhibition by valine. The gene encoding the large AHAS subunit from *E. coli* is structurally described in the art and functionally described in the specification having the catalytic activity as found on page 6 of the specification. The instant specification also describes particular mutations in SEQ ID NO:1 that encode a small subunit exhibiting reduced valine inhibition (see Table 1 on page 24) when coupled with the catalytic large subunit. In this Table, only a single example of being

"free from inhibition by L-valine" is demonstrated by pILVH612 (several mutants are described as having reduced valine feedback inhibition). The instant claims are drawn to a genus of DNA encoding **any** small subunit from any source having this same function without any particular structural limitations (limited point mutations relative to SEQ ID NOs:1/2 are required in Claims 4-5). The limited example of particular mutations in SEQ ID NO:1 having this function do not adequately describe the entire genus because the structure of other members of the genus cannot be predicted based on the disclosure since common characteristics among members of the genus have not been described.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

17. Claims 3 and 6 are rejected under 35 U.S.C. § 102(b) as being anticipated by Guardiola *et al.* (see IDS #3). The instant claims are drawn to DNA and bacterial host cells thereof wherein the DNA encodes the large and small subunits of acetohydroxy acid synthase isozyme (AHAS) III from *E. coli* wherein the AHAS is free from valine inhibition and the AHAS is catalytically active.

Guardiola *et al.* teach a mutant of *E. coli* MI261, called strain 1, with a phenotype named *ilv*B619, having low levels of enzyme activity without valine inhibition (see pages 536-537, bridging paragraph). Strain 1 inherently contains the DNA encoding the AHAS subunits.

The Examiner notes that this mutant strain is noted as having no activity in the instant specification (see page 22, lines 5-8); this is inconsistent with the teachings of Guardiola *et al.* While the enzyme activity is low compared to wild-type, any enzymatic activity meets the limitations of Claim 3.

18. Claims 1 and 6 are rejected under 35 U.S.C. § 102(b) as being anticipated by Smith *et al.* (Complete Genome Sequence of *Methanobacterium thermoautotrophicum* ΔH: Functional Analysis and Comparative Genomics. J. Bacteriol. (1997) 179(22): 7135-7155). The instant claims are drawn to DNA and bacterial host cells thereof wherein the DNA is from *E. coli* (with the additional inclusion of several mutations) and encodes a mutated small subunit of acetohydroxy acid synthase (AHAS) having a mutation at position 17 to a residue other than a serine.

Smith *et al.* teach a gene from *Methanobacterium thermoautotrophicum* encoding an acetolactate synthase, also know as acetohydroxy acid synthase, small subunit (see page 7144, right column of Figure 4) called the *ilvH* gene. This gene sequence, when mutated by a series of substitutions, deletions, insertions, etc. (as prescribed in the instant specification on page 9), is equivalent to SEQ ID NO:2, the sequence originating from *E. coli*, and contains a difference at position 17 from a serine (S) to a glutamine (Q) (see attached alignment).

Other Notable Art

19. The following references are noted to complete the record but are not used as prior art against the pending claims:

a) Grimaldi *et al.* (A mutation affecting the valine sensitivity of the acetohydroxyacid synthase III isozyme in *E. coli* K-12. Biochem. Biophys. Res. Comm. (1981) 101(4): 1233-1240) teach an ilv-751 mutation at a locus other than *ilvH* (see page 1233) that reduces, but does not abolish valine feedback inhibition of AHAS III (see page 1238, Table 3).

Allowable Subject Matter

20. DNA encoding the Gly14Asp mutation and the Asn29Lys/Gln92TAG mutations in the *E. coli* AHAS III small subunit (*ilvH* gene - SEQ ID NO:2) are known in the art by virtue of Vyazmensky *et al.* (see IDS #3) and Guardiola *et al.* (see IDS #3), respectively. However, Claims 1 and 2 require a mutation at Ser17, which residue is not identified in the art as crucial for valine feedback inhibition in the *E. coli ilvH* gene. Moreover, while a combination of data presented in Vyazmensky *et al.* and Guardiola *et al.* could produce a mutant of Gly14/Asn29 or Gly14/Gln92 (Claim 4), there is no suggestion or motivation in the art to render such a combination obvious. The Examiner suggests claiming DNA encoding particular mutants, wherein the mutants are described by SEQ ID NO:2 with particular mutations, i.e., Gly14, Ser17, etc. to avoid written description and clarity issues.

Conclusion

21. Claims 1-8 are rejected for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (703) 305-1229. The examiner can normally be reached on Monday through Friday, from 8:30am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

KMK
October 21, 2002